III. REMARKS

Claim status

Claims 1, 3-15 17-22 are in the case. Claim 1 has been amended.

Specification objection - 35 U.S.C. § 112, first paragraph

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and. failing to provide an enabling disclosure.

Claims 1, 3, and 17-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant does not describe or enable any method or kit in which the patient is administered elastase peptides to obtain antibodies or a method to determine overall elastase content by detecting the "existence" of antigen-antibody reactions in an immunized patient as now claimed. Applicant is requested to direct the Examiner's attention to specific passages where support for these newly recited limitations can be found in the specification as filed or is required to delete the new matter.

Applicant has amended claim 1 to more closely track the

specification, *inter alia*, at page 4, 2nd paragraph, thus obviating this ground for objection.

Contrary to the statement of the Examiner that the specification only teaches polyclonal antibodies, at page 3, last sentence and at page 5 of the specification, third line from the bottom of the description, it is taught that the invention can to be carried out by the use of mono- and polyclonal antibodies. The production of monoclonals is taught at page 6, first paragraph. For someone skilled in the art it is routine work to produce polyclonal as well as monoclonal antibodies when he is in possession of the antigens.

Furthermore, the claims have been amended to refer to "pancreatic elastases(iso-enzymes)" rather than "all known pancreatic elastases" thus bringing them into compliance with the specification.

Claim Rejections - 35 U.S.C. 112, first paragraph

Claims 1, 3, 6-11, and 17-24 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record, that the specification contains subject matter which was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention,

For the reasons of record, the issue is whether the disclosure describes and supports the ability of the recited peptides to elicit antibodies that bind singly, or in combination, and function for determination of elastase isoforms I, II, and III in a body fluid sample.

Contrary to the examiner's assertion, the disclosure amply describes the technique for ascertaining whether there is a disturbance in pancreatic function.

Claim Rejections - 35 U.S.C. 112, second paragraph

Claims 1, 3, 10, 18, and 20-24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 and claims dependent thereupon, the examiner states the interrelationships of the components and steps of the method are entirely unclear to the point that one would not know what is determined or how to perform the method.

As interpreted by the examiner, the invention as claimed, apparently involves immunizing a patient with at least peptide pairs to elicit antibodies that bind to elastases I, II, **or** III for the intended use of determining overall content of elastases I, II, **and** III presumably by merely detecting the existence and quantity of an antigen-antibody complex in some undefined manner. It is not clear if applicant intends some determination of reaction in the patient as being encompassed. There is no connection between inducing antibodies in the patient and any assay.

Applicant disagrees with the examiner's statement. Amended claim 1 now reads:

> "Diagnostic procedure for identification of a disorder of pancreatic function in a patient

comprising **determining (iso-enzymes) in the patient's serum, secretions or excretions** by means of an immunochemical system using one or more antibodies selected from the group consisting of polyclonal antibodies raised against any of the following synthetic peptides …"

The presence of antibodies in the **serum, secretions or excretions is the indicator of a** disorder of pancreatic function.

Claim Rejections 35 U.S.C. § 102(b)

Claims 6-8, 10, and 22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sziegoleit et al. (Clin. Biochem. 22: 79, 1989) in light of the instant disclosure.

The examiner utilizes Sziegoleit et al. as teaching a sandwich enzyme-linked immunosorbent assay for diagnosis of pancreatitis or pancreatic cancer by determining pancreatic elastase 1 using polyclonal antibodies. The antibodies were elicited in several animal species, including rabbits, with complete elastase 1 which, in light of the instant disclosure, comprises the peptides in their entirety (i.e. an immunogenic portion) as instantly claimed.

As more extensively set forth below Sziegoleit et al. do not teach the antibodies which are the essence of applicant's surprising contribution to the art.

Claims 6-8, 10, 11, and 22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Scheefers et al. (USP 5,622,837)

in light of the instant disclosure .

The examiner utilizes Scheefers et al. (USP 5,622,837) as teaching determinations of pancreatic elastase 1 in serum and stool samples as indicative of pancreatic disease. The reference teaches determinations with sandwich immunoassays involving antibodies, preferably monoclonal, elicited to different epitopes of the protein, including the use of antibodies specific for particular epitopes therein elicited by immunization with purified enzyme or fragments thereof, as a sensitive alternative to radioimmunoassay. In light of the instant disclosure, highly purified pancreatic elastase 1, as taught in the reference as an immunogen (see e.g. ¶ bridging col. 2-3) for elicitation of the antibodies, comprises the peptides in their entirety (i.e. an immunogenic portion) as instantly claimed. The reagents for the method can be incorporated into a kit.

As more extensively set forth below Scheefers et al. do not teach the antibodies which are the essence of applicant's surprising contribution to the art.

The core point of the invention is the antibodies that are generated from specific peptides selected from areas of the elastase. The antibodies are used to determine if human elastase or parts of it in present in the patients serum, secretions or excretions. The presence or absence of human elastase allows diagnosis of a disturbance in pancreatic function or not.

The main important feature of the invention are the novel antibodies.

Applicant has cancelled the term "overall content". In the

time the invention was made, only elastase 1 was known. Today it is knowledge, that there are several isoforms existing (please see the publication Rose SD MacDonald, enclosed). Each antibody according to the invention binds to one of these isoforms but there is at least one antibody binding to each isoform. This is the reason the term "overall content" was used at the time of the invention and might be inappropriate today.

The antibodies are new and special, because they are directed against highly specific areas of all types of the human pancreatic elastases.

The antibodies of the prior art are not as highly specific as the antibodies of present invention. People who have disturbances in pancreatic function often get food supplements with parts of pancreas achieved from pork or cattle. This comprises elastases from these animals. The antibodies of the prior art also binds to those non-human elastases and therefore gives false results.

The antibodies of present invention only bind to human elastases. This is confirmed by the article from Dr. T. M. Rossi, please find enclosed.

The antibodies of present invention are very short but nevertheless highly specific. When elastase is digested, the antibodies of present invention are still able to recognize and bind to them.

The antibodies of the prior art are not able to bind as specific and reliable as the antibodies of present invention to the fragments. In this connection applicant does not agree with

the Examiner, that the digestion of elastase in the intestinal tract contradicts the art. The specification, on page 2, discloses that elastase "displays extraordinary stability during the passage through the intestines". This is in view of other enzymes like chymotrypsin and amylase.

Applicant again states that elastase has extraordinary stability compared to amylase or chymotrypsin. The reason might be that elastase also acts as a carrier protein.

But this doesn't mean that elastase is not undergoing degradation at all. As a protein, of course it is digested, if this would not happen, we would die. This is established knowledge of each person skilled in the art and therefore the specification is comprehensible.

Also Dr. Weiss describes in his abstract that elastase does not undergo significant degradation. The same is explained by further different experts in the other publications. Applicant is enormously astonished that the Examiner does not understand this explanation.

Factual evidence is given by several publications describing comparative experiments with the claimed system and tests of prior art.

The studies of Prof. Keim (enclosed again), might be the most extensive and significant. He shows the differences in binding between the most common tests of the state of the art and present invention in comparative experiments.

Furthermore during the FDA certification process also

comparative studies with antibodies of the state of the art were performed. They all confirm the results of Prof. Keim.

Therefore also please find Erickson et al., Garcia et al. and an overview about several further publications, which clearly show the advantages of the claimed antibodies according to the invention over the tests of prior art.

There is also another misunderstanding concerning the Weiss publication. Elastase II a and II b and III a and Ill b are existing in samples of the patients. The detection of one of the isoforms is sufficient for the analyses of the disease. A mixture of several different antibodies can enhance the accuracy of the test but is not necessary.

Dr. Weiss describes only the test with four of the claimed antibodies. As already explained, the antibodies are highly specific. So each antibody binds to one specific area which only exists in human pancreatic elastases. Enclosed a list of the antibodies according of the invention and the elastases they bind to.

The antibodies used by Dr. Weiss only react with elastases III a and III b, which is shown in his abstracts (also enclosed again). It is very important that they don't react with elastase I because this one is not expressed in adult human beings. The tests of Dr. Weiss show that the used antibodies only react with the corresponding isoforms. As well, it is shown that the antibodies do not cross react with pig elastase.

The objection of the Examiner, that the inventor was not in

possession of the claimed invention is also not comprehensible to applicant.

The test has been on the international market since the year 2000.

The German, European and Japanese patents are already granted.

Since 2003 the product is also distributed in the US market. Together with the partner JOU Medical Products, a FDA certification for the product was achieved.

In the year 2009, 3347 tests were sold worldwide, 884 of them were distributed in the US by applicant's U.S. partner. With those 884 tests 71,000 samples of patients with suspected pancreatic insufficiency could be analyzed in the US Applicants of our tests in the U.S. are f.e. LabCorp (Burlington), Doctor's Data Inc. (St. Charles), ARUP Institute for Clinical and Experimental Pathology (Salk Lake City), Johns Hopkins Bayview Medical Center (Baltimore), Mayo Clinic (Rochester).

These facts show that the claimed Elastases-ELISA based on those antibodies is very successful on the market and that the invention closes a gap in the diagnoses of pancreatic insufficiency.

The publication of Dr. Weiss was only possible after applicant provided him with the claimed antibodies. Dr. Weiss was not allowed to start with his work until the patent applications were filed in several countries.

Against the background of the given information applicant has

surely understand that and cannot comprehend the Examiner's repeated objections and rejections of the claims and specification.

Encl.: - Rose SD MacDonald RJ
- Dr. T. M. Rossi et al.
- Dr. Weiss
- Erickson et al.
- Garcia et al.
- Prof. Dr. Keim ClinLab 2003
- overview publications
- list of the antibodies

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Respectfully submitted,

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